

which it is bound. The portion of the target sequence bound to the PNA tag complement is the tag and the target sequence contains additional polynucleotide sequences which are considered the sequence specific portion.”¹

Thus, apparently the examiner is equating the elements of the claimed invention with the structures shown in the Norton reference as follows:

| Claim Element | Norton Structure |
|---|--|
| Target specific portion of probe | Portion of target sequence not used as a tag |
| Tag portion of probe | Portion of target sequence hybridized with PNA probe |
| Tail portion of mobility modifier | Staph. nuclease |
| Tag complement portion of mobility modifier | PNA oligomer |

B. The Legal Standard. To anticipate a claimed invention, a single reference must anticipate all of the essential elements of the invention.²

C. Analysis. As reproduced above, the examiner states that “The portion of the target sequence bound to the PNA tag complement is the tag *and the target sequence contains additional polynucleotide sequences which are considered the sequence specific portion.*” However, according to the present application, the target specific portion of the probe is “capable of sequence-specific binding to a target nucleic acid sequence...”³ But, in the Norton structures, the “target sequence” is a double-stranded target, i.e., plasmid pUC 19⁴. Therefore, the “additional polynucleotide sequence” of the Norton structure is a double-stranded nucleic acid and is therefore NOT capable of sequence-specific binding to a target nucleic acid, and therefore may not be considered a “target-specific portion” of a probe according to the present invention.

Thus, because the structures set forth in the Norton reference do not include a probe having a “target specific portion for sequence-specific hybridization”, the Norton reference does not anticipate all of the essential elements of the claimed invention, and

¹ Office Action mailed February 9, 2001 at paragraph 3.

² *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 802 F.2d 1367 (Fed.Cir. 1986)

³ Specification at page 10 lines 8-12.

⁴ Norton at page 442, column 1, 6 lines from the bottom.

therefore may not be found to anticipate the claimed invention under 35 U.S.C. §102. Consequently, the rejection is improper and should therefore be withdrawn.

Rejections Under 35 U.S.C. § 103

At paragraph 4, the examiner has rejected claims 1-12 under 35 U.S.C. §103(a). The rejection is respectfully traversed in light of the following remarks.

A. The Rejection. Claims 1-12 were rejected as being unpatentable over Barany et al., WO 97/31256 ("Barany") in view of Grossman et al., U.S. Pat. No. 5,514,543 ("Grossman").

As understood by applicants, the reasoning behind the Examiner's rejection is as follows:

"It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have attached the tag complements taught by Barany et al. to the mobility modifiers taught by Grossman et al."⁵ because,

1. "Grossman et al. expressly teaches that their method 'allows a plurality of target sequences to be assayed in a single-assay format, with rapid identification of sequences according to the mobilities of different polymer chains associated with the sequence-specific labeled probes.'⁶

2. "The combination of the methods of Grossman et al. with those of Barany et al. would have provided an improved method which utilized a sensitive detection system taught by Barany et al. and a rapid identification system as taught by Grossman et al."⁷

B. The Legal Standard.

In establishing the obviousness of a claimed invention, the Examiner bears the initial burden of establishing the *prima facie* case of obviousness. Obviousness can only be established by modifying or combining the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found in either (1) the references themselves, or, (2) in the knowledge generally available to one of ordinary skill in the art⁸. The mere fact that the prior art may be modified in a manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.⁹

⁵ Office Action mailed February 9, 2001 at page 4 lines 16-19.

⁶ Office Action mailed February 9, 2001 at page 4 line 20 to page 5 line 1.

⁷ Office Action mailed February 9, 2001 at page 5 lines 4-7.

⁸ MPEP 2143.01 and *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

⁹ *In re Gordon et al.*, 221 USPQ 1126 (Fed. Cir. 1984).

The Federal Circuit has often addressed the application of the above standard, and cautioned Examiner's and courts against bypassing the requirement for finding a suggestion in the art for a combination of references, and instead simply using a hindsight reconstruction of the prior art based on the teachings of the application's specification to make a combination which renders the claimed invention obvious.

For example, in the case of *In re Dembiczak*, the invention was directed to a large bag made of orange plastic and decorated so as to resemble a Halloween pumpkin when full. The invention was rejected by the Examiner (and the Board of Patent Appeals and Interferences) for being obvious based on a combination of references: a first reference to an orange garbage bag, and a two references describing a method of making a paper bag pumpkin by stuffing a paper bag with newspapers, painting it orange, and then painting facial features on its outside surface with black paint (Holiday and Shapiro references). In rejecting the invention, the board determined that,

“[t]he only difference between the invention presently defined in the independent claims on appeal and the orange plastic trash bags of the prior art and the use of such bags resides in the application of the facial indicia to the outer surface of the bag...the missing facial indicia elements were provided by the Holiday and Shapiro references’ description of painting jack-o-lantern faces on paper bags.”¹⁰

In reversing the Board, the Federal Circuit provided a lucid discourse on how not to apply a combination-of-references rejection, and the importance of requiring the Examiner or court to show **evidence** of a suggestion for the combination, and not to rely merely on “conclusory statements.”

“Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.”

“Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement of a showing of the teaching or motivation to combine prior art references.”

“Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor’s disclosure as a

¹⁰ *In re Dembiczak*, 50 USPQ2d 1614 at 1616 (Fed. Cir. 1999).

blueprint for piecing together the prior art to defeat patentability—the essence of hindsight.”

“Broad conclusory statements regarding the teaching of multiple references, standing alone, are not “evidence.”

“[t]he obviousness analysis in the board’s decision is limited to a discussion of the ways that the multiple prior art references can be combined to read on the claimed invention... Yet this reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the Holiday and Shapiro references teach or suggest their combination with the conventional trash or lawn bags to yield the claimed invention.”¹¹

Magistrate Smalkin of the United States District Court, District of Maryland colorfully illustrated the reasoning behind the above analysis when he said, “[y]ou cannot claim that the existence of a unicorn should be obvious from taking a trip to the zoo and seeing a horse and a white rhinoceros in adjacent cages. It takes a spark of inventiveness to look at the horse and then look at a white rhinoceros and then conceive the idea of a white horse with a horn.”¹²

C. Analysis.

The present rejection is a clear case of a combination of references based on a hindsight reconstruction of the prior art using the claimed invention as a blueprint. As in *Dembiczak*, the Examiner has identified elements of the claimed invention in the prior art, but has not provided sufficient evidence of a teaching, suggestion or motivation in the prior art to support a rejection based on combining the teachings of the prior art to produce the claimed invention.

The Barany reference concerns a nucleic acid detection method using an array of support-bound oligonucleotides in which an oligonucleotide probe is hybridized to a solid support through a tag / tag-compliment interaction, and the hybridized probe is detected while hybridized to the solid support. Specifically, Barany teaches,

“[t]he detection of nucleic acid sequence differences in nucleic acids using a ligation phase, a capture phase, and a detection phase. The ligation phase utilizes a ligation detection reaction between one oligonucleotide probe which has a target sequence-specific portion and an **addressable array-specific portion** and a second oligonucleotide probe having a target sequence-specific portion and a detectable label. The capture phase

¹¹ *Id.* At 1617 and 1618.

¹² *The Laitram Corporation et al. v. Cambridge Wire Cloth Company*, 226 USPQ 289, 293 (D.Md. 1985).

involves **hybridizing the ligated oligonucleotide probes to a solid support** with an array of immobilized capture oligonucleotides at least some of which are complementary to the addressable array-specific portion. The labels of ligated oligonucleotide **probes hybridized to the solid support are detected** during the detection phase.”¹³

There is no teaching, suggestion, or motivation in Barany to perform a method in which a probe having a tag is contacted with a mobility modifier having a tag complement to form a probe/mobility modifier complex, and the probe/mobility modifier complex is analyzed using a mobility-dependent analysis technique.

The Grossman reference teaches a qualitatively different method of analyzing nucleic acid sequences in which oligonucleotide probes having polymer chains attached thereto are separated by electrophoresis or chromatography and the separated fractions are individually detected. The Grossman method does not involve an oligonucleotide array, hybridization of an oligonucleotide onto an oligonucleotide array, or the detection of an oligonucleotide that has been hybridized onto an oligonucleotide array. Rather, it involves a method that obviates the need for oligonucleotide arrays entirely. Moreover, there is no teaching, suggestion, or motivation in Grossman to perform a method in which a particular polymer chain (or mobility modifier) is associated with a particular probe by using a probe having a tag and a mobility modifier having a tag complement that binds to the tag, thereby forming a probe/mobility modifier complex. While Grossman describes the genius of mobility-dependent nucleic acid analysis using mobility modifiers, it does not teach or suggest the species of improvement claimed in the present application.

In the obviousness rejection based on a combination of Barany and Grossman, the Examiner has provided no indication of where in Barany, or in Grossman, or in knowledge generally available to one of ordinary skill in the art, there is some teaching, suggestion, or motivation to combine the teachings of Barany and Grossman along the lines of the present invention. The Examiner has completely sidestepped the requirement of a showing of the teaching or motivation to combine the references. Instead, what the Examiner offers are broad statements regarding the teachings of Barany and Grossman, and not evidence of a teaching, suggestion, or motivation to combine the references.

This rejection is a clear case of a combination of references based on a hindsight reconstruction of the prior art. Because the Examiner has failed to show where in the prior art or in the knowledge generally available to one of ordinary skill in the art there is a teaching, suggestion or motivation to combine Barany and Grossman along the lines of the present invention, the rejection is improper and should therefore be withdrawn.

¹³ Barany at page 1 lines 12-21. (Emphasis supplied.)

Rejections for Double Patenting

At paragraph 7, the examiner has rejected claims 12-25 for double patenting. However, these claims are not pending in the present application. (Taking into account the examiner's renumbering of claims 1-11 (including claim "6.1") to be claims 1-12.) Therefore, this rejection is improper and should be withdrawn.

III. CONCLUSION

In view of the foregoing remarks, applicants submit that the claims pending in the present application are in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at 650-638-5846.

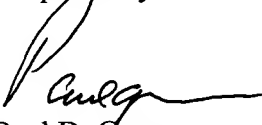
IV. CONDITIONAL PETITION FOR TIME EXTENSION and FEE AUTHORIZATION

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account number 01-2213.

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Respectfully submitted,


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